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Multi-analyte Biochip (MAB) Based on All-solid-state Ion-selective Electrodes (ASSISE) for Physiological Research

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Abstract

Lab-on-a-chip (LOC) applications in environmental, biomedical, agricultural, biological, and spaceflight research require an ion-selective electrode (ISE) that can withstand prolonged storage in complex biological media¹⁻⁴. An all-solid-state ion-selective-electrode (ASSISE) is especially attractive for the aforementioned applications. The electrode should have the following favorable characteristics: easy construction, low maintenance, and (potential for) miniaturization, allowing for batch processing. A microfabricated ASSISE intended for quantifying H⁺, Ca²⁺, and CO₃²⁻ ions was constructed. It consists of a noble-metal electrode layer (*i.e.* Pt), a transduction layer, and an ion-selective membrane (ISM) layer. The transduction layer functions to transduce the concentration-dependent chemical potential of the ion-selective membrane into a measurable electrical signal.

The lifetime of an ASSISE is found to depend on maintaining the potential at the conductive layer/membrane interface⁵⁻⁷. To extend the ASSISE working lifetime and thereby maintain stable potentials at the interfacial layers, we utilized the conductive polymer (CP) poly(3,4-ethylenedioxythiophene) (PEDOT)⁷⁻⁹ in place of silver/silver chloride (Ag/

AgCl) as the transducer layer. We constructed the ASSISE in a lab-on-a-chip format, which we called the multi-analyte biochip (MAB) (**Figure 1**).

Calibrations in test solutions demonstrated that the MAB can monitor pH (operational range pH 4-9), CO_3^{2-} (measured range 0.01 mM - 1 mM), and Ca^{2+} (log-linear range 0.01 mM to 1 mM). The MAB for pH provides a near-Nernstian slope response after almost one month storage in algal medium. The carbonate biochips show a potentiometric profile similar to that of a conventional ion-selective electrode. Physiological measurements were employed to monitor biological activity of the model system, the microalga *Chlorella vulgaris*.

The MAB conveys an advantage in size, versatility, and multiplexed analyte sensing capability, making it applicable to many confined monitoring situations, on Earth or in space.

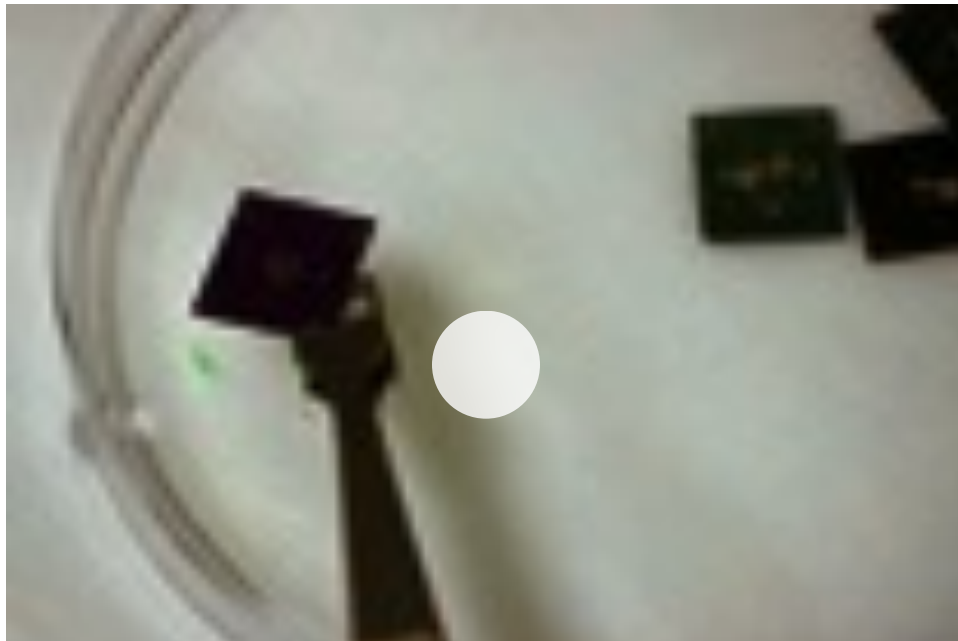
Biochip Design and Experimental Methods

The biochip is 10 x 11 mm in dimension and has 9 ASSISEs designated as working electrodes (WEs) and 5 Ag/AgCl reference electrodes (REs). Each working electrode (WE) is 240 μm in diameter and is equally spaced at 1.4 mm from the REs, which are 480 μm in diameter. These electrodes are connected to electrical contact pads with a dimension of 0.5 mm x 0.5 mm. The schematic is shown in **Figure 2**.

Cyclic voltammetry (CV) and galvanostatic deposition methods are used to electropolymerize the PEDOT films using a Bioanalytical Systems Inc. (BASi) C3 cell stand (**Figure 3**). The counter-ion for the PEDOT film is tailored to suit the analyte ion of interest. A PEDOT with poly(styrenesulfonate) counter ion (PEDOT/PSS) is utilized for H^+ and CO_3^{2-} , while one with sulphate (added to the solution as CaSO_4) is utilized for Ca^{2+} . The electrochemical properties of the PEDOT-coated WE is analyzed using CVs in redox-active solution (*i.e.* 2 mM potassium ferricyanide ($\text{K}_3\text{Fe}(\text{CN})_6$)). Based on the CV profile, Randles-Sevcik analysis was used to determine the effective surface area ¹⁰. Spin-coating at 1,500 rpm is used to cast ~2 μm thick ion-selective membranes (ISMs) on the MAB working electrodes (WEs).

The MAB is contained in a microfluidic flow-cell chamber filled with a 150 μl volume of algal medium; the contact pads are electrically connected to the BASi system (**Figure 4**). The photosynthetic activity of *Chlorella vulgaris* is monitored in ambient light and dark conditions.

Keywords: Bioengineering; Issue 74; Medicine; Biomedical Engineering; Chemical Engineering; Electrical Engineering; Mechanical Engineering; Chemistry; Biochemistry; Anatomy; Physiology; Miniaturization; Microtechnology; Electrochemical Techniques; electrochemical processes; astrobiology; Analytical; Diagnostic and Therapeutic Techniques and Equipment; Investigative Techniques; Technology; Industry; Agriculture; electrochemical sensor; all-solid-state ion-selective electrode (ASSISE); conductive polymer transducer; poly(3,4-



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Protocol

1. Preparation of Poly(3,4-ethylenedioxythiophene):Poly(sodium 4-styrenesulfonate) (PEDOT:PSS) Electropolymerization Solution for H^+ and CO_3^{2-} Ions

1. Add 70 mg poly(sodium 4-styrenesulfonate) (Na^+PSS^-) to 10 ml deionized (DI) water and vortex until completely dispersed (approx. 10 sec).
2. Add 10.7 μ l 3,4-ethylenedioxythiophene (EDOT) to the solution in 1.1 and vortex until solution is completely mixed.

2. Preparation of Poly(3,4-ethylenedioxythiophene):Calcium sulphate (PEDOT:CaSO₄)

Electropolymerization Solution for Ca^{2+} Ions

1. Add 136 mg calcium sulphate (CaSO_4) to 10 ml DI water and vortex; the solution will not completely disperse and appears milky.
2. Add 10.7 μl EDOT to the solution in 2.1 and vortex until completely mixed.

3. Electropolymerization of PEDOT-based Conductive Polymer

1. A Bioanalytical Systems Inc. (BASi) C3 cell stand (**Figure 3**) and an EC epsilon potentiostat/galvanostat are used to form the electrochemical cell for electropolymerization. Place the EDOT:PSS electropolymerization solution in the electrochemical cell and nitrogen bubble for 20 min to remove dissolved oxygen.
2. Now clip a platinum-gauze at the counter electrode position of the electrochemical cell. Then clip the MAB at the working electrode position of the electrochemical cell with the working electrodes facing the platinum-gauze. Adjust the MAB depth so that only the circular electrodes are submerged in the PEDOT:PSS electropolymerization solution. Avoid solution contact with the square electrical contact pads.
3. Place a BASi saturated silver/silver chloride (Ag/AgCl) electrode in the reference electrode position of the electrochemical cell. Make sure that the reference electrode is not in between the working and counter electrodes.
4. For PEDOT:PSS deposition: Bubble the electrochemical cell for 20 min, and use the EC epsilon potentiostat/galvanostat to run a single cyclic voltammogram from 0V - 1.1V with a scan rate of 20 mV/sec on a $\pm 100 \mu\text{A}$ scale.
5. For PEDOT: CaSO_4 deposition: Bubble the electrochemical cell for 20 min, and use the EC epsilon potentiostat/galvanostat to run chronopotentiometry at 814 nA for 30 min.

4. Cyclic Voltammetry of PEDOT-based Polymer Conjugates in $\text{K}_3\text{Fe}(\text{CN})_6$

1. Perform steps 3.1- 3.3 above.
2. Use the EC epsilon potentiostat/galvanostat to run single cyclic voltammograms from -653 mV to 853 mV with varying scan rates of (25, 50, 75, 100, 125, 150, 175, 200) mV/sec on a $\pm 10 \mu\text{A}$ scale.

5. Surface Functionalization Protocol

1. Deposit conductive polymer conjugate specific for the ions of interest as in Step 3.
2. Apply ion-selective membrane as in Step 6.

6. Application of Ion-selective Membrane

1. Center the MAB on the vacuum spinner chuck.
2. Deposit 100 μl membrane onto the center of the MAB and run.
3. Spin-coat ion-selective membrane with a spin coater at 1,500 rpm for 30 sec with a 5 sec ramp up and down.
4. Vacuum the spin-coated MAB for 30 min and bake the chip in an oven at 70 $^{\circ}\text{C}$ for 20 min.

7. Calibration of PEDOT-PSS Conductive Polymer Conjugate with pH and Carbonate (CO_3^{2-}) Ion-selective Membrane

1. Condition the MAB overnight in 10 μM sodium bicarbonate (NaHCO_3) and 5 mM potassium chloride (KCl) in algal media.
2. Insert the MAB into the microfluidic flow-cell chip holder.
3. Inject 5 ml test solution with initial pH value or concentration (e.g. pH 4 or 10 μM for CO_3^{2-}). Remove bubbles from the flow-cell chip holder.
4. Place the flow-cell chip holder onto the flow-cell electrical fixture.
5. Open the EC epsilon software and enter open-circuit potential (OP) mode. Set the time to 300 min, the voltage scale to $\pm 1\text{V}$, and the cutoff frequency to 10 kHz, and record the value every 2 sec.
6. Let the MAB stabilize (look for a flat line) before continuing with the calibration process.
7. Once the MAB is stabilized, flush the flow cell with test solution and inject the next concentration to be calibrated (pH 5 or 25 μM CO_3^{2-}). Make sure that no bubbles are allowed to enter the flow cell. Repeat steps 7.5 and 7.6 for pH 6, 7, 8, and 9 or CO_3^{2-} concentrations of 50, 75, 100, 250, 500, 750, and 1,000 μM .
8. After the last concentration has run, remove the MAB and dry with nitrogen air.
9. Place the MAB back into fresh conditioning solution until next use.

8. Calibration of PEDOT: CaSO_4 Conductive Polymer Conjugate in CaCl_2

1. Condition the MAB overnight in 7 ml of 0.1 M CaCl_2 and 10 μM NaNO_3 .
2. Follow steps similar to 7.2 - 7.10. In step 8.3, replace carbonate test solution with an initial concentration of 0.01 mM CaCl_2 . Repeat for test-solution concentrations of 0.05, 0.1, 0.5, 1 and 10 mM.

Representative Results

An example of a cyclic voltammogram (CV) result of PEDOT:PSS and its corresponding cathodic peak current (i_p) vs. the scan rate ($v_{1/2}$) are shown in **Figures 5a** and **5b** respectively. PEDOT: CaSO_4 at various scan rates and its cathodic peak current are not shown. Using Randles-Sevcik analysis¹⁰, the effective surface areas of the solid contact PEDOT:PSS and PEDOT: CaSO_4 without ion-selective membrane were found to be $4.4 \times 10^{-11} \text{ cm}^2$ and $5.8 \times 10^{-11} \text{ cm}^2$, respectively. These values are relatively small in comparison to previous reported electrodes owing to the electrode size

being ~130 times smaller than the electrode size reported from our research group ¹¹. Note that the MAB electrode effective surface area could be enhanced by modifying the surface with nanomaterials ¹¹.

Calibration results for ISEs based on PEDOT:PSS polymer conjugates in algal media with pH ranging from 4 to 9 after 20 days storage in the algal medium are shown in **Figure 6**. The variation in the slope profile could be due to the complex biological medium (ATCC medium: 1.0 L Bristol's solution and 1.0 g Protease Peptone (BD Diagnostic System, Sparks, MD, USA), which has fouling compounds and interfering salts that can affect measurements. The purpose of the work is to test the ASSISE capability to acquire measurements in the actual cell-culture environment.

We turn now to the calibration results for PEDOT:PSS in carbonate (CO_3^{2-}) solution with a concentration range of 0.01 mM to 1 mM in both algal biological medium and algal biological medium buffered at pH 8.5 (**Figure 7**).

Measurements are performed at pH 7.8. The inset shows the change in concentration, with a lowering of the slope with the buffered solution. The results show the pH dependence of the carbonate-selective electrode. These results are meaningful if one considers the existence of different carbonate species in the dissolved form; specifically H_2CO_3 (carbonic acid), HCO_3^- (bicarbonate,) and CO_3^{2-} (carbonate). The pK_{a1} value for carbonic acid to bicarbonate form is 6.4 while the pK_{a2} value from bicarbonate to carbonate is 10.4. When the pH is greater than the pK_a , the species is in its deprotonated form, while when the pH is lower than the pK_a , the species is in its protonated form. Since measurements are made at pH 7.8, most species are in the bicarbonate form. The increment in voltage correlates to the increment in the carbonate species. Because of the pH dependence of the carbonate concentration, one must consider this dependency when carrying out measurements in biological media. Measurements using the MAB with a PEDOT:PSS-based ISE in 150 μl algal medium containing microalgal *Chlorella vulgaris* at pH 7.8 are shown in **Figure 8**. We note a 30 mV change which correlates to a decade change in carbonate concentration in alternating light and dark conditions. These results can be explained by considering the physiological activity of microalgae during photosynthesis. Under dark conditions the algae remain in a state of dormancy where no photosynthetic activity occurs. This can be seen in the graph where the mV reading remains constant and close to the initial baseline reading. Once the algae are exposed to light, they are actively undergoing photosynthesis; hence a decrease in HCO_3^- and CO_3^{2-} levels is observed as expected. In terms of a mV reading this should correspond to an increase in voltage since the levels of HCO_3^- and CO_3^{2-} levels are decreased. Calibration results for PEDOT: CaSO_4 in CaCl_2 solution with concentrations ranging from 0.01 mM to 1 mM are shown in **Figure 9**. The PEDOT: CaSO_4 is used to pattern a 3D electrode format for measuring calcium levels from the fern spore *Ceratopteris richardii*; those results are not presented here. The results show an almost Nernstian slope profile for 30 mV per decade change in Ca^{2+} concentration. The calibration result will be used to measure the calcium current levels in germinating fern spores. Those results are not presented here.

For all measurements, the measurement linear range is tailored to fit the range required for the application.

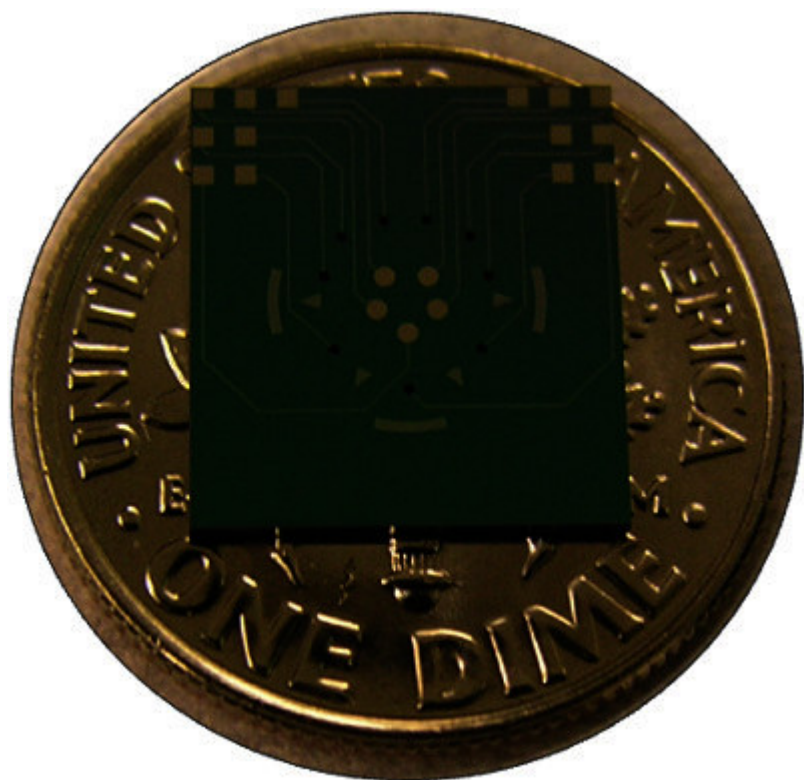


Figure 1. Multi-analyte biochip (MAB). The

biochip consists of multiple working and reference electrodes.

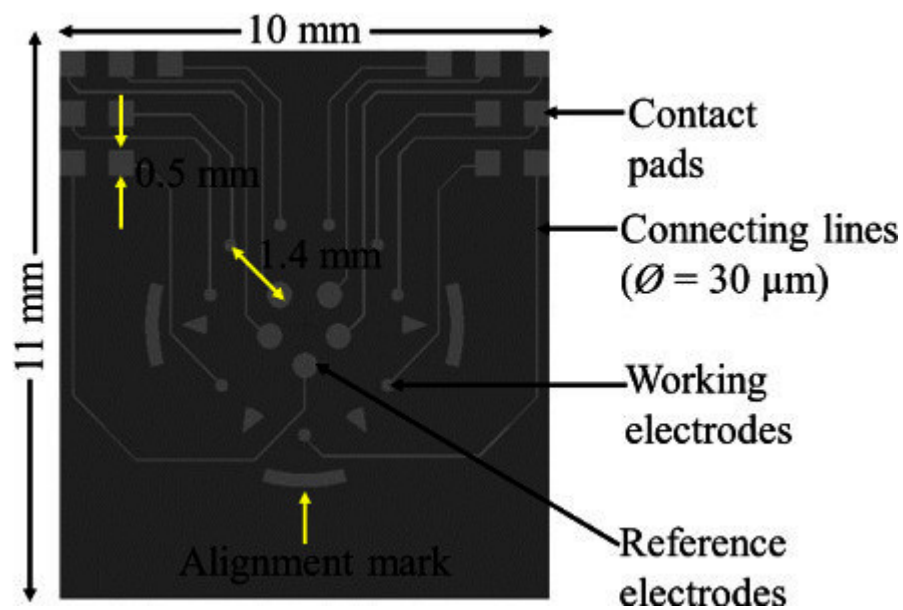


Figure 2. MAB design schematic. The

MAB is a 10 x 11 mm biochip which consists of 9 Pt electrodes ($\varnothing = 240 \mu\text{m}$) intended as ISE working electrodes (WEs), and 5 Pt ($\varnothing = 480 \mu\text{m}$) electrodes intended as reference electrodes (REs). Two sets consisting of three electrodes share a reference electrode (RE), while the remaining 3 have their own RE. The sets of three WEs with shared REs are intended for potentiometric measurement, while the rest are intended for amperometric measurement. The WEs and its corresponding REs are equally spaced at 1.4 mm apart. These electrodes are connected to Pt contact pads (0.5 x 0.5 mm) located at one end of the biochip.

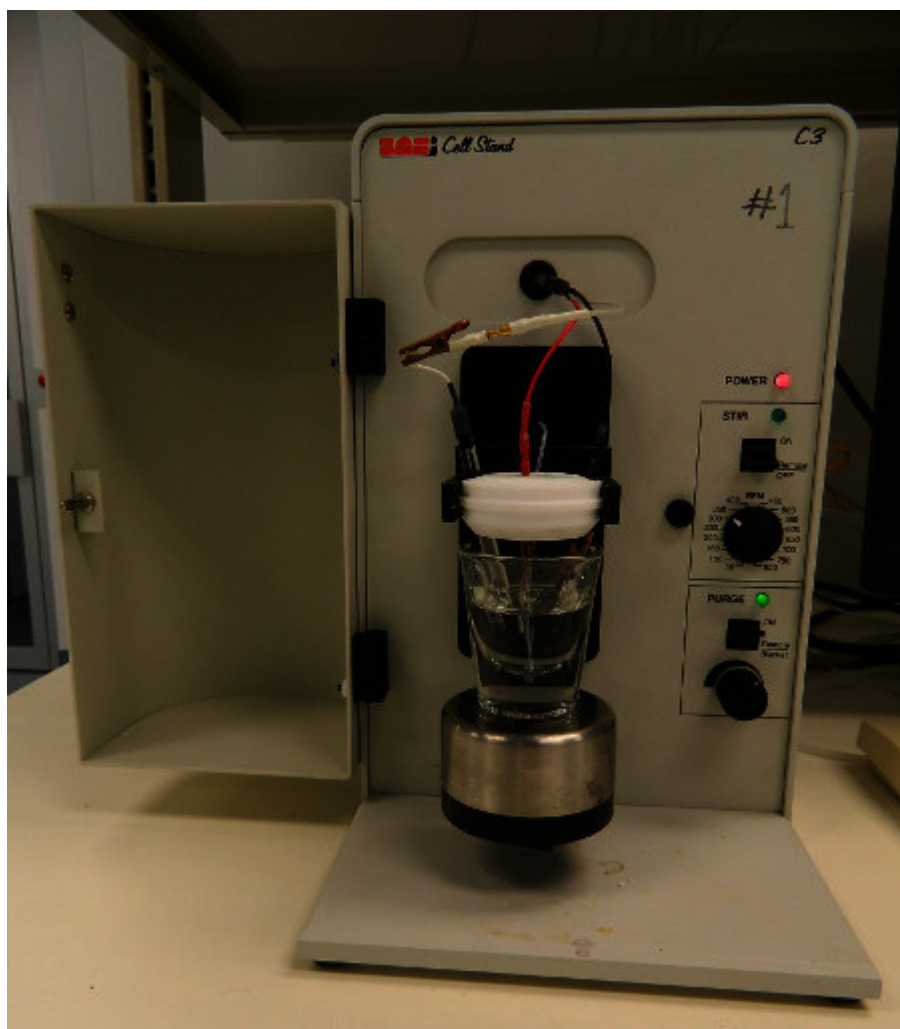


Figure 3. BASI cell stand three-electrode potentiostat/galvanostat system. The BASI is electrically connected to the microfluidic flow-cell chamber and records voltage measurements in real-time.

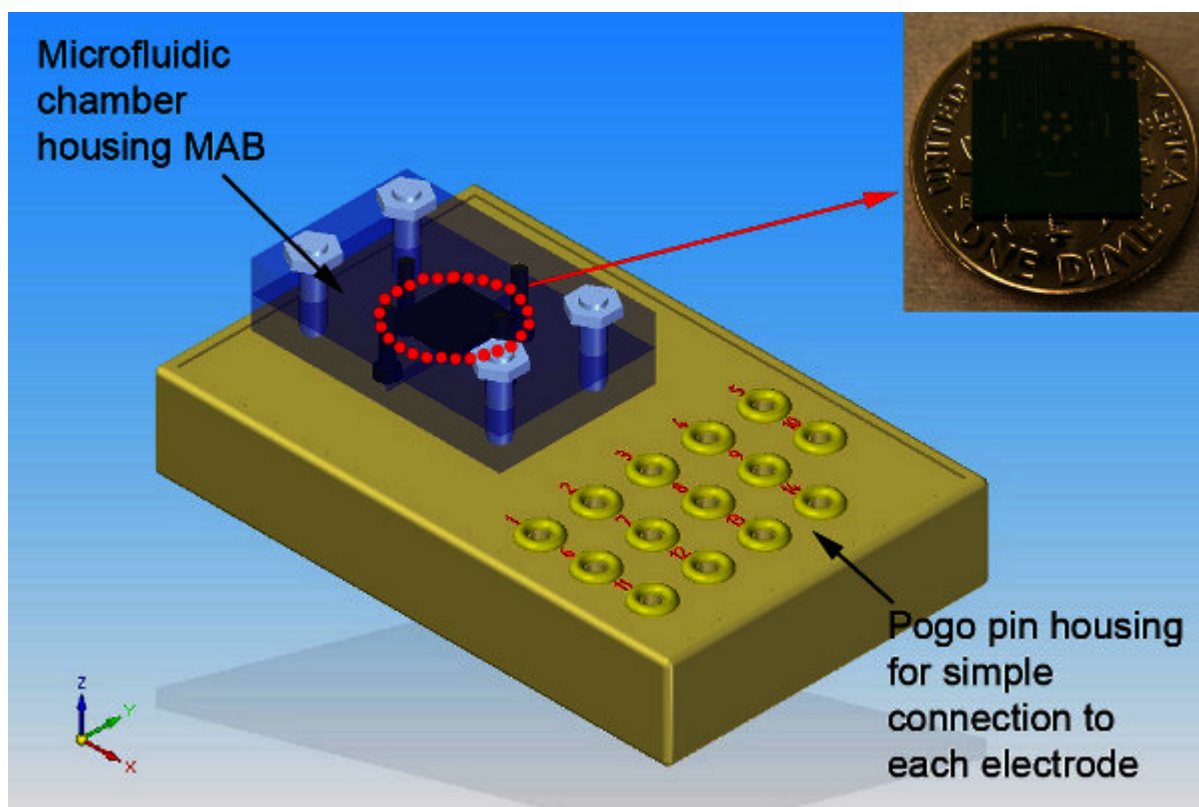


Figure 4.

Microfluidic flow-cell chamber. A syringe is connected at both the inlet and outlet of the microfluidic chamber to push measurement fluid on the biochip.

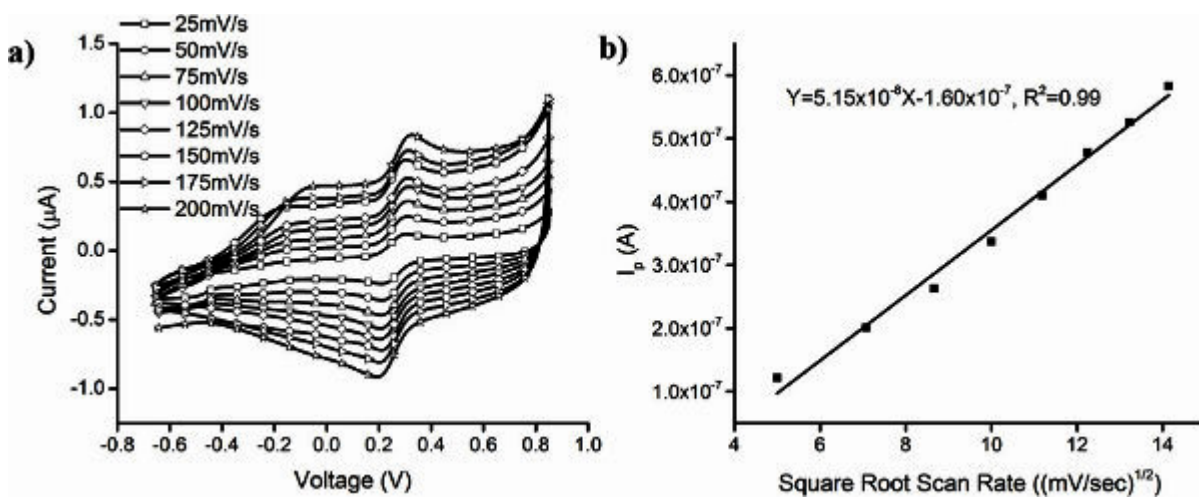


Figure 5. (a)

Cyclic voltammetry profiles at various scan rates and (b) the corresponding cathodic peak vs. the scan rate for Randles-Sevcik analysis. Based on Randles-Sevcik analysis, the effective surface areas of the electrodes were calculated to be $4.4 \times 10^{-11} \text{ cm}^2$ and $5.8 \times 10^{-11} \text{ cm}^2$ for PEDOT:PSS and PEDOT: CaSO_4 respectively. [Click here to view larger figure](#).

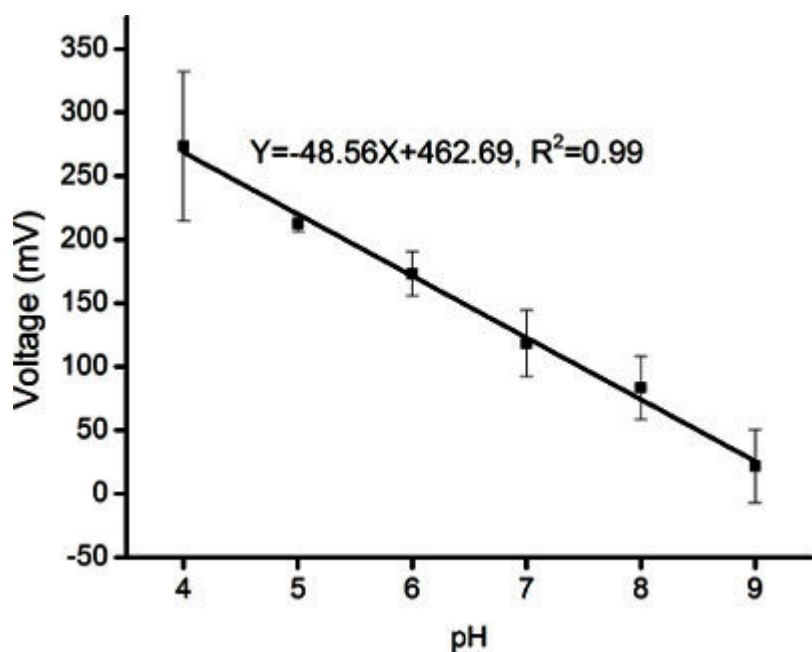


Figure 6. Calibration profile for MAB ISEs

based on PEDOT:PSS in solution with increasing pH for 4 different measurements conducted with the same biochip over the course of 28 days. The results show a larger error range at pH 4 due to the fluctuation of H^+ ions at the lower detection limit.

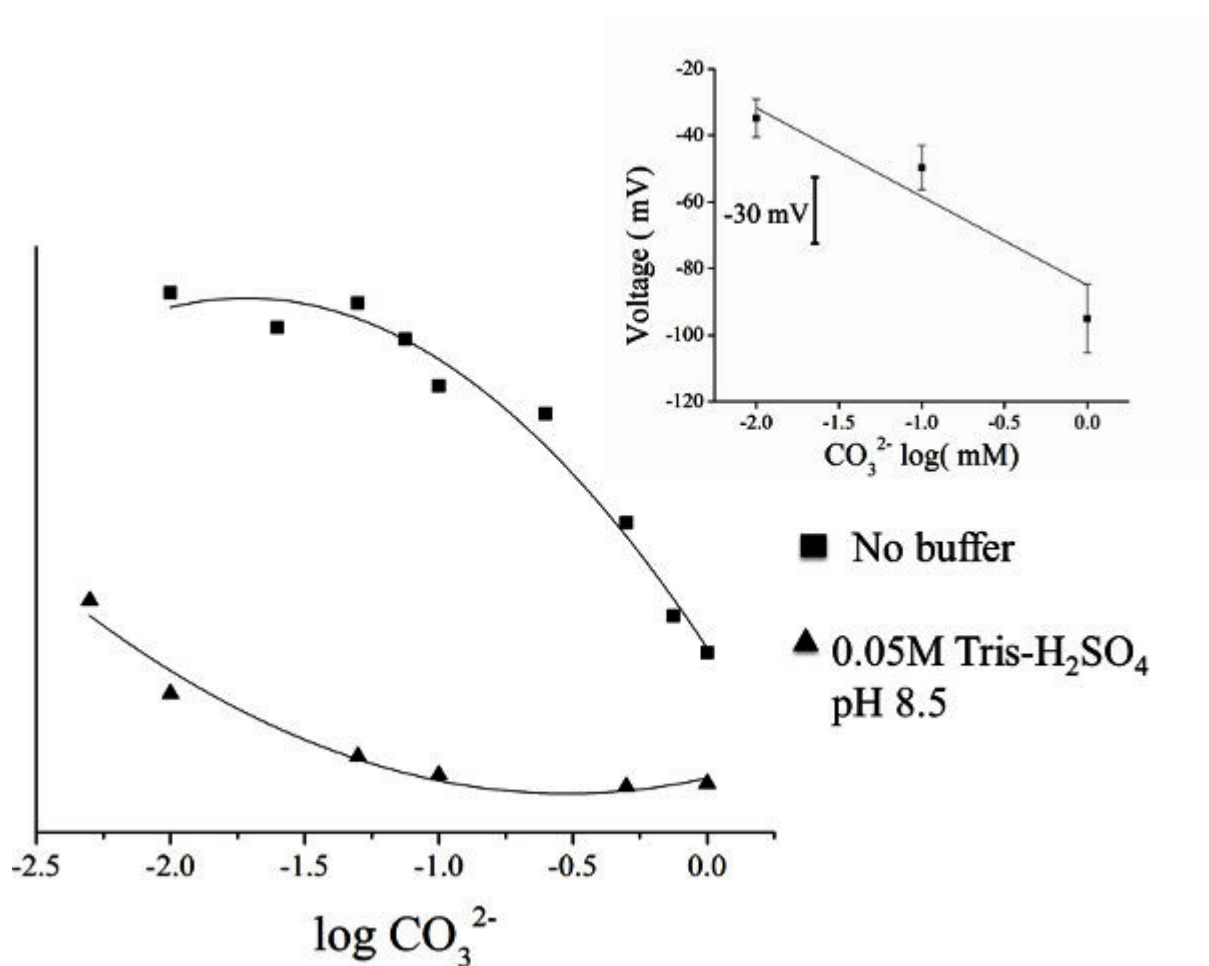


Figure 7.

Calibration profile for MAB ISEs based on PEDOT:PSS in $CaCO_3$ solution with increasing concentration of CO_3^{2-} in both algal medium and buffered algal medium at pH 8.5. The results show the effect of pH on CO_3^{2-}

sensing due to the availability of several carbonate species at different dissociation constant (pKa) values - H_2CO_3 (carbonic acid), HCO_3^- (Bicarbonate,) and CO_3^{2-} (carbonate). Since MABs are to perform measurements in natural samples, calibration are made with unbuffered algal media, showing a slope of -30 mV per decade change in CO_3^{2-} concentration.

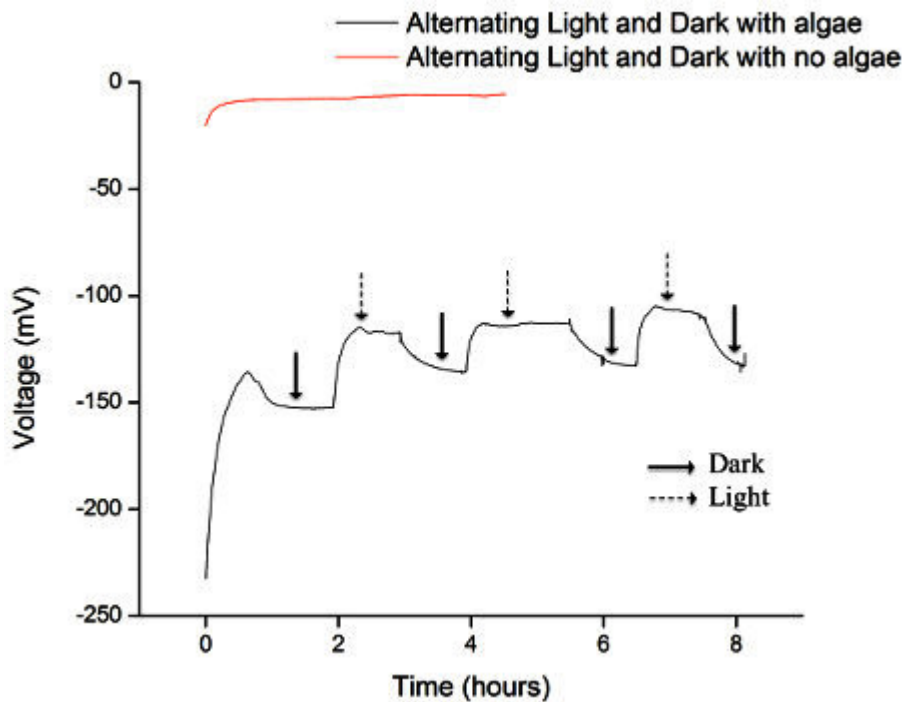


Figure 8. CO_3^{2-} concentration

measurement with biological model *Chlorella vulgaris* in ambient light and dark conditions showing a 30 mV change. This ~30 mV change correlates to a decade change in CO_3^{2-} concentration. A control with only algal media shows no response, indicative of a functional biochip.

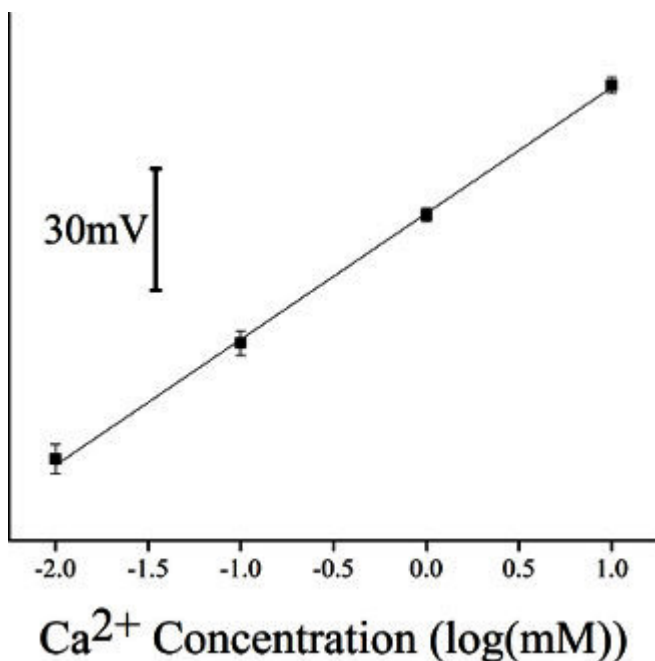


Figure 9. Calibration profile for MAB ISEs based on

PEDOT:PSS in CaCl_2 solution with increasing concentration. The results show an near-Nernstian slope profile for

divalent cation at 30 mV per decade change in Ca^{2+} concentration.

Chemical Components for H⁺ Membrane	Weight %	Company	Catalogue number
polyurethane (PU)	23.1 %	Sigma Aldrich	81367-5G
polyvinylchloride (PVC)	9.9 %	Sigma Aldrich	81387-250G
potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (KTFPB)	0.5 %	Sigma Aldrich	60588-10MG
hydrogen ionophore I (H ⁺ ionophore)	1 %	Sigma Aldrich	95292-100MG
bis(2-ethylhexyl) sebacate (DOS)	65.5 %	Sigma Aldrich	84818-25ML
Chemical Components for Ca²⁺ Membrane	Weight %		
polyurethane (PU)	10.0 %	Sigma Aldrich	81367-5G
polyvinylchloride (PVC)	19.0 %	Sigma Aldrich	81387-250G
potassium tetrakis[4- chloropheny) borate (KTpCPB)	0.7 %	Sigma Aldrich	60591-100MG
calcium ionophore I (Ca ²⁺ ionophore)	1.0 %	Sigma Aldrich	21193-100MG
bis (2-ethylhexyl) sebacate	69.3 %		84818-25ML
Chemical Components for CO₃²⁻ Membrane	Weight %		
polyurethane (PU)	17.8 %	Sigma Aldrich	81367-5G
polyvinylchloride (PVC)	18.2 %	Sigma Aldrich	81387-250G
Tridodecylmethylammonium chloride (tmACl)	1.0 %	Sigma Aldrich	91661-100MG

Carbonate ionophore IV (CO_3^{2-} ionophore)	9.0 %	Sigma Aldrich	21856-1EA
Bis(2-ethylhexyl) sebacate	54.0 %	Sigma Aldrich	84818-25ML

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Table 1. Ion-selective membrane chemical composition. All membrane compositions are dissolved in solvent (cyclohexanone) at 10 % wt/volume. For all membrane compositions, 4.3 mg of silicon tetrachloride (Sigma Aldrich, catalog number: 215120) was added for 100 mg of dry components.

Discussion

The MAB biochip consists of ASSISEs that are constructed from an ISM atop a PEDOT-based CP conjugate transduction layer on a Pt electrode, the combination of which transduces the ionic concentration of interest to a measurable electrical signal. A stable electrode potential is defined by both the CP layer and the ISM layer. Both layers also determine the working lifetime of the MAB and the quality (noise, drift) of the measured electrical signal.

PEDOT is especially attractive as a transduction layer owing to both its ionic and electronic properties (when in its oxidized form). PEDOT has the capacity for high redox capacitance to minimize conductive electrode polarizing effects; we have measured its stable redox potential at $153 \text{ mV} \pm 6$ vs. Ag/AgCl. This characteristic is necessary for the potential stability of the ISE, which uses a solid internal contact ¹². The PEDOT:PSS CP conjugate is used as a transducer for small monovalent cations (*e.g.* H^+) and divalent anions (*e.g.* CO_3^{2-}). The nonlinear slope profile of the carbonate-selective electrode is due to its dependence on pH. For measurements with microalgae, simultaneous measurement must be made for H^+ and CO_3^{2-} ions. The result for CO_3^{2-} measurements is similar to that of conventional electrodes ¹³ and similar planar electrodes that are much larger in dimension ¹⁴. Hence, the electrode geometry reported on here does not alter potentiometric properties. Furthermore, when the solution is buffered at pH 8.5, the slope profile for decade change in CO_3^{2-} concentration decreases from -30 to -17 mV. This could be explained by the fact that H_2CO_3 , HCO_3^- , CO_3^{2-} , and dissolved CO_2 all coexist in aqueous solutions and this equilibrium depends upon pH. More studies are needed to explore this aspect of the carbonate ion results. For measurements with divalent cations, we replace the PSS counter-ion with CaSO_4 salt, resulting in a PEDOT: CaSO_4 polymer conjugate. We believe that excess divalent Ca^{2+} cation from the dissolved CaSO_4 within the polymer conjugate prevents binding of the measured Ca^{2+} from the sample solution.

Electrochemical methods (cyclic voltammetric and galvanostatic) are used to tailor the physical and electrochemical

properties of the PEDOT-based polymer conjugate. These electrochemical methods of deposition are useful for rapid construction of ASSISEs. The application of ASSISEs is not limited to ion sensors; the CP conjugates can be functionalized with biomolecules and the MAB can function as a biosensor. Owing to the long functional working lifetime demonstrated with the ISEs for H⁺ ions, the MAB is suitable for applications that require long-term monitoring in a complex biological liquid medium environment. Hence, it has the potential to be useful in *in-vivo* biomedical research and long-term monitoring of ions in drug screening.

Disclosures

We have nothing to disclose.

Acknowledgments

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